FIFRA SCIENTIFIC ADVISORY PANEL (SAP)

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1   DR. DURKIN: It seems to me that -- Chris has kind of put his

2   finger on it here. You folks aren't approaching this from an RFD point

3   of view, but you are looking at it as a margin of exposure. It seemed

4   to me that where Chris might be going, and please correct me if I'm

5   wrong here, is that if the stability, the confidence intervals narrowed

6   at a higher effect level, that might not be a bad thing to do.

7   But then you would simply want to say, well, we're not going to

8   accept an MOE of 100, but maybe an MOE of something higher.

9   And that seems to be a reasonable approach, which is not to say

10   I think that there is going to be any consensus here that you want to

11   do anything differently.

12   I mean, the ED10 is a little disquieting. It's not bringing down

13   the house. You are not going to have folks lined up down on the

14   floor. So it may be reasonable to have an ED10 with an MOE of 100.

15   It could be reasonable to pick an ED50 perhaps and, depending on how

16   the data are, and simply say as a judgmental approach that now we're

17   not happy with an MOE of 100 anymore, but we're going to increase

18   that by some factor.

19   And I don't know that there is a truly analytical way to get at

20   that. I think that may just involve somebody probably down at that

21   end of the table going out on a long limb.

1   But the gist, I think, of our comments here is that what you

2   have done appears to be reasonable. There are other things that you

3   can think about, but there is nothing really wrong here.

4   DR. KENDALL: I can accept that.

5   DR. BRIMIJOIN: One more comment, then we should turn to

6   some of the other questions.

7   DR. PORTIER: I'm just going to highlight one of the things in

8   my comment, which I have written down. And that is, an objective

9   criteria for choosing a benchmark dose.

10   All I'm asking for is some objective criteria for that. And then

11   we can talk about the risk characterization later. But that's the thing

12   to look for, is why choose 10 or 5 or 1.

13   DR. BRIMIJOIN: The next point that is raised here is a

14   question about the expression of inhalation exposure in the same units

15   as the oral doses.

16   That was something that EPA was told to do by the previous

17   meeting. They have done it.

18   Does everyone agree on that point?

19   THE MEMBERS: Yes.

20   DR. BRIMIJOIN: So that brings us to consideration of the

21   impact of individual animal data instead of summary information.

1   And Dr. Durkin had a comment on that.

2   DR. DURKIN: Well, I would like to beat my dead horse, if I

3   could, and just get some clarification for my own benefit and the

4   benefit of others who are going to be looking at this method.

5   When we got together, I guess a couple of years ago, I made a

6   relatively impassion plea for the use of individual animal data. You

7   people would not accept this study if that data weren't there.

8   I made the point that it is not that hard to get. And it is not that

9   hard to treat. You have been at this for a long time. I honestly think

10   you are going to be at it for a lot longer.

11   And it seemed quite reasonable to me. I did work that in to the

12   SAP recommendations in the report.

13   The last time we got together, I thought I heard somebody at

14   EPA essentially say that it can be analytically demonstrated that if we

15   use the mean and some measure of variability associated with that

16   mean, it can be analytically demonstrated that it's just not going to

17   make any difference at all.

18   And I think I heard a murmur of approval from those

19   statistically knowledgeable around the table here. And again, I will

20   point out that I am not now nor have I ever been a statistician,

21   mathematician or anything else like that. I am uneasy when I read

1   your response -- and overall, again, I think you have done a great job

2   in responding to our criticisms, but this one you essentially quoted our

3   last report which had a bit of a milk/toast thing about individual

4   animal data are nice, but it probably wouldn't make that much

5   difference. And I think we might have been echoing back what we

6   heard.

7   I have tried to understand better, read a few things with all

8   sorts of Greek characters that gave me the willies.

9   We do have a lot of really good stat people here. I just want

10   someone to whack me on the head to tell me that I'm wrong. But this

11   is my understanding. If the measurements from the individual animals

12   are reasonably symmetrically distributed about the model

13   measurement, it is probably not going to make a great deal of

14   difference either in the central estimate of exposure or perhaps even in

15   your assessment of the errors that might be associated with your dose

16   response model.

17   If on the other hand that is not the case, and for something like

18   acetyl cholinesterase inhibition, I'd rather suspect that especially in

19   the lose dose region, if you have a group of 10 animals, you are

20   probably going to see eight of them that are just honky dory and two

21   that start heading south, that it still could be worth looking at the

1   individual animal data, at very least to better explicate to people like

2   myself why it is not generally necessary.

3   And at least do it for one or two chemicals to show us that it

4   isn't necessary.

5   But I really think you have to document it better and in some

6   way qualify it so that if this huge effort that you have undertaken is

7   indeed used, as I suspect it will be used as a model or other similar

8   assessments, there are some guidelines.

9   And it may well be the case that you can analytically

10   demonstrate that we never have to look at this data. I doubt that's

11   true.

12   There probably have to be some guidelines given. And I think

13   you should do a fuller job discussing in the document why in this case

14   you have elected not to take that additional step and, again, educate

15   me and perhaps put in at least a single example of here is a case where

16   we use the individual animal data as well as the group data and it just

17   doesn't make a lot of difference.

18   So I remain very skeptical about the decision. It is about the

19   only criticism I have of what you have done to respond to us, but

20   about this decision to ignore the individual animal data.

21   I'll get off the soap box now.

1   DR. KENDALL: I would welcome a response.

2   DR. SETZER: There are a number of issues surrounding the

3   individual animal data.

4   One of them is the one you have alluded to. And it has to do

5   with sort of the shapes of distributions and the nature of the response.

6   I basically agree with your concerns about that.

7   The other issue, and that was one that people -- I think we

8   talked about a lot in the last SAP review, had to do with the issue that

9   for the blood measurements, plasma and red blood cell, we had

10   repeated measures on those data sets.

11   And in fact in that case, we can't even do a legitimate analysis

12   of the data without individual animals.

13   Imagine my joy to hear that we have decided to work on brain

14   instead of plasma and red blood cell. We have eliminated that.

15   DR. DURKIN: It doesn't get you off the hook.

16   DR. SETZER: I understand that it doesn't get us off the hook.

17   But it changes the relative priorities of various sorts of analyses.

18   Part of the problem has to do with the relative efforts involved

19   in getting individual animal data for all these chemicals. The data are

20   there, my understanding is, on paper stored away somewhere.

21   Turning those into something that we can analyze is doable, but

1   labor intensive and can take time. And I think my understanding is we

2   couldn't get it done before our deadlines.

3   However, we do have the sort of data sets you are talking

4   about. We have an example data set. At the moment I can't give you

5   the details. It is several chemicals and at least more than one study at

6   least for some of the chemicals.

7   We do have easily -- already extracted the individual animal

8   data. And it is our intention to analyze those data. We just didn't get

9   to it yet.

10   DR. DURKIN: In terms of some of the problems that you have

11   talked about in optimizing your model, the thing that I have found at

12   least with kinetic studies is your optimization may head south if you

13   use group measurements.

14   If you do pull in the individual animal studies, a lot of times

15   your models will optimize better.

16   I'm not making a guaranty here of course. But I'm just trying to

17   encourage the agency to at least think about it.

18   I know that it is clerical work. And I appreciate that. And you

19   have to QC it. And there is all sorts of troubles.

20   But it would certainly make me feel better to at least see in the

21   body of your report we don't use individual animal data because it just

1   ain't necessary, or whatever you want to say and to see at least one

2   example to get this guy off our back. It just didn't make a whole lot of

3   difference.

4   But I do suspect that with cholinesterase it will give you

5   perhaps an insight into what is going on with the animals that could be

6   useful.

7   DR. KENDALL: Dr. Durkin, I think you have made your point.

8   And it's well taken.

9   DR. LOWIT: Can I make one more response? We thought

10 about this a lot.

11   And Woody is correct. The vast majority of the data we have

12 right this second is in paper in shelves and everything else and have

13 made efforts to make images of the pages and everything else.

14   We have roughly between 15 and 20 for which we have been

15 able to take TIF images and convert them to electronic data sets. And

16 honestly, I ran out of time.

17   DR. KENDALL: Thank you.

18   Dr. Portier?

19   DR. PORTIER: I'll briefly reiterate a point we made at the last

20 meeting just so it is on the record again this time.

21   And that we would encourage the agency to prospectively think

1   about beginning to collect all of this data electronically for any future

2   studies so that you can do individual animal data analyses.

3   Not necessarily retrospectively for this one, but clearly there is

4   some advantage to doing that in the future.

5   DR. KENDALL: Good point. Very good.

6   Dr. Brimijoin, I know you are going to make it through this first

7   question.

8   DR. BRIMIJOIN: Yes. We're getting close here.

9   The last question is about the derivation of oral doses from the

10   actual dietary intake rates.

11   Again, that's a cryptic summary of a recommendation from

12   September. And I take it that the point was measure actual rates.

13   Don't just guess what levels are being ingested.

14   Is the panel satisfied with the response in the present document?

15   THE MEMBERS: Yes.

16   DR. MCCONNELL: I would only add one thing. This is a small

17   point, but it's one that bugs me all the time when I see it, is that

18   exposure and dose are misused quite often in this document.

19   And I think it would for the purists in the crowd it would

20   certainly help that when you talk about dose you are talking about

21   what really is absorbed into the body versus exposure, what we get in

1   our food and what we breathe and what we get on our skin.

2   And there are two different concepts. For toxicologists, it is

3   one of those pet peeve things.

4   DR. BRIMIJOIN: Turn this over to the next group?

5   DR. KENDALL: Yes, Dr. Conolly?

6   DR. CONOLLY: I mentioned this earlier, but I got to read the

7   draft cancer guidelines last month. And in the guidelines is a very

8   explicit delineation of what they call exposure. I think it is applied

9   dose and internal dose.

10   And it might be useful, I think, for the agency as a whole to

11   harmonize their terminology perhaps in these terms. It is very clearly

12   worked out in the cancer guidelines.

13   DR. KENDALL: Any further comments from the panel, Dr.

14   Portier, for Question 1A?

15   DR. PORTIER: I'm going to assume that we have the ability to

16   go beyond the list of items here to some of our other recommendations

17   that were done and comment on your handling of those other

18   recommendations.

19   Is that agreeable to you?

20   DR. KENDALL: Yes.

21   DR. PORTIER: There was one more point which I raised in my

1   questions but which I will now formally comment on.

2   And that is the CELs and the use of the CELs in this analysis

3   and the comparison of the CELs to the benchmark dose numbers.

4   I still believe that this is inappropriate. I still frown upon the

5   agency using NOAELs and LOAELs in any context. I believe the

6   regression based techniques indicate to you when in fact you don't

7   have sufficient information to make a dose response analysis. And to

8   use LOAELs and NOAELs in those situations are just going to be

9   somewhat misleading.

10   There are a few pathological cases where you might make a

11   good argument for a LOAEL or NOAEL. But I think as a general rule

12   I would prefer regression analysis.

13   In addition, there are some, I'll call them, throwaway

14   statements, for lack of a better term. In the risk assessment document,

15   they talk about inability to fit some of these data to dose response

16   models, which I find difficult to believe in looking at the data that I

17   was looking at.

18   So again, I would encourage you to extend the regression

19   techniques across all data sets.

20   And failure to do that should tell you something about the

21   information you have in hand.

1   DR. KENDALL: Dr. Reed?

2   DR. REED: I think I was the one who made that comment

3 during the last meeting, that last request about deriving oral doses

4 from actual dietary intake rates.

5   My comment was in the context of when we were looking at

6 where is the beginning of this, 21 days or 28 days or any further. And

7 at the time I understood that the dose was calculated based on an

8 average body weight and consumption rate in a long term study, for

9 example, a two-year study.

10   And it isn't quite sure right now to me if that had been looked at

11 since then or -- I was under the impression that there was no further

12 analysis since September's meeting about the data sets.

13   Am I correct on that?

14   I mean, did the agency go back and did reanalyze or reenter the

15 dose response based on --

16   DR. LOWIT: I believe the document number is III B -- I'm

17 pretty sure it is 4.

18   There is a section in that document where we did a pilot and --

19 somewhat of a pilot using subsets of the studies where each time point

20 the dietary intake from a window close to the time of the

21 cholinesterase was measured was used as opposed to the whole study

1   average. And that is in that section as a pilot.

2   And I assume when they -- this side of the room nods their head

3   that that was okay, that they saw that.

4   DR. REED: That's what I thought. But then it was confusing

5   when there was a statement about half an hour ago saying there is no

6   reanalysis of data. And then I was confused about that.

7   So there was. Okay.

8   The other thing is that I probably don't have as strong a feeling

9   against using NOAEL as comparison point when you don't have

10   enough data, but I was also under the impression that with the oral

11   studies there is situations where, because we're using brain

12   cholinesterase inhibition now, that you might not have as many data

13   sets and there is situations where you only have one data set with the

14   oral data.

15   So how does that differ from the inhalation and dermal studies

16   having lack of data? I understand that in certain situations you just

17   can't model it. But I also would like to echo Chris's comment about if

18   it is possible to see how they model.

19   I understand that not every case you have the luxury of doing

20   that even with one data set.

21   DR. KENDALL: Dr. Bull?

1   DR. BULL: I saved this until last because it's not the most

2   important thing.

3   One of the things that I missed as I read through this, and I had

4   to read some parts of it very quickly, I would have liked -- I realize

5   you don't have all the pharmacokinetic mechanistic information you

6   need on all 29 compounds, but as you are going through these

7   processes, as did you when you dealt with the shoulder on the

8   response, it would be useful to kind of check your assumptions against

9   the data that are there.

10   One of the things I saw no discussion of is -- 4 is more of an

11   example.

12   The degree of cholinesterase inhibition at any given point in

13   time reaches a steady state based on the rate at which react with the

14   enzyme and the rate which is either regenerated or resynthesized.

15   And it would have been nice to just kind of touch base with that

16   and say, well, in the rat we know that the enzyme is regenerated with a

17   half line of X, Y or Z.

18   Some of the -- maybe your shoulder even might relate to the

19   fact that somebody's phosphate esters are going to hydrolyze at

20   different rates than others depending on the structure of the phosphate

21   ester -- and so forth.

1   If you could find -- if could kind of spend a little bit of time,

2   not a lot, because you are still going to have to go back, as I think you

3   did to the descriptive data in the end anyway, it would just make those

4   of us that are a little bit more inclined towards mechanism if you bless

5   that part of the effort.

6   It's just a general comment.

7   DR. KENDALL: Thank you. For the panel in terms of moving

8   forward here, we will go onto Question 1 B, complete that and take a

9   break.

10   Then I would like, because we are doing very well, Mr. Lewis

11   here has recommended that we proceed to the next question, which

12   would have been scheduled for tomorrow morning, and to achieve that

13   question today, leaving us to begin in the morning with the assessment

14   of food exposure. That's where I would like to be.

15   And there is some consideration as recommended to me by Mr.

16   Dorsey as trying to finish all the panel's deliberation by Thursday

17   evening instead of going into Friday.

18   I want you thinking about that, EPA.

19   So we will proceed as deliberately as needed, whatever time is

20   needed, but this is a possibility. And it would, I think, be more

21   efficient in time and resources if that was achieved.

1   Nevertheless, let's go to Question 1 B. And that has been

2   presented to us. And Dr. Heeringa, would you lead off, please, sir?

3   DR. HEERINGA: Let me for the record just read the question,

4   Question 1 B.

5   DR. KENDALL: That will be fine.

6   DR. HEERINGA: Several of these issues were addressed by the

7   application of the nonlinear mixed effect model for combining

8   cholinesterase data.

9   In addition, EPA utilized the profile likelihood method for

10   estimating horizontal asymptotes when they could not be estimated

11   jointly with other parameters. Please comment on the use of these

12   statistical procedures in the dose response assessment of the

13   organophosphate pesticides.

14   I'm going to lead off with a few comments.

15   DR. KENDALL: Yes. Thank you, Dr. Heeringa.

16   DR. HEERINGA: The question of the nonlinear mixed effect

17   model, and that's a long title for a statistical procedure, let's break it

18   down for a moment, it is quite clear that the nonlinear component

19   here, even if we assume normality of the error terms, essentially what

20   we're saying is that the conditional means of these expected responses

21   are nonlinearly functions of a series of parameters.

1   So that piece is quite obvious. And I think that has been

2   recognized for a long time.

3   But one thing about nonlinear modeling of any sort is that the

4   data must be adapted to estimate the points of inflection in these

5   nonlinear models.

6   Just my sort of naive exposure to this is that a lot of the dose

7   response studies that we appear to be dealing with appear to be more

8   optimized. In other words, their spacing of dosings in the underlined

9   studies themselves appear to be more optimal for linear estimation

10   such as probe it type dose response regression functions.

11   And looking through the actual graphs that were presented,

12   which were very, very helpful for me because I'm pretty much a visual

13   person on a lot of statistics, it is quite clear that for a lot of the things

14   that we're dealing with, such as the shape and displacement parameters

15   in the expended model, that a lot of those parameters in the current

16   studies are being estimated in zones of observation where we have

17   very little data.

18   If you look at it, a lot of times we get data points preceding the

19   inflection points represented either by the parameters in the basic

20   model or the S and D parameters in the expanded model.

21   And that's not something that the EPA can do anything about.

1   However, I think in encouraging, if we move on to use these models in

2   cumulative risk assessment for organophospates, I think it behooves

3   all of us to begin looking at measurement strategies that are more

4   optimal for estimating these particular models.

5   I'm going to leave comments about the expanded models for the

6   next question.

7   The second is really the mixed effect in that here we're talking

8   about mixtures affixed and random effects.

9   My only comment here is that mixed effect models are very,

10   very useful. And I think that this is an appropriate adaptation of

11   mixed effect models.

12   Now, we have to remember what we -- when we include random

13   effects in models, you essentially -- random effects are included to

14   reflect effects of things that pretty much are random in the observation

15   process, like the animals themselves, their responsiveness, whether

16   you get a particular batch of rats that has a particular disposition to

17   cholinesterase inhibition.

18   We expect that to vary about some mean for the standard series

19   of rats that are being used or other animals that are being used, the

20   particular preparations, which might be errors at the local level, but

21   they may vary about calibration standards or other forms of

1   measurement error.

2   One of the things that we're including in these models as a

3   random effect are essentially the data sets within the studies.

4   And I asked the question this morning about what distinguishes

5   those. And the point comes up that duration may distinguish one data

6   set from another.

7   And I had asked the question if we're treating data sets as

8   random effects, we're really treating duration as a random effect. Is

9   duration a random effect or a fixed effect in modeling cholinesterase

10   inhibition.

11   These are sort of rhetorical questions which I ask myself. And

12   they are not criticisms. But you need the minimum of two

13   observations to estimate a variance.

14   And when we get into these random effects, one of the

15   principles here, and without looking at power E calculations, but we

16   need to have a significant number of observations on the random effect

17   itself.

18   And if that is a study, we need to have I believe more than two

19   studies to be pretending they are random effects. Otherwise, we could

20   say we have effective a particular individual or a particular teacher.

21   But if it is Mr. Smith and Ms. Jones and those are the only two

1   observations we have, we really have fixed effect to Mr. Smith and Ms.

2   Jones. And we're averaging that.

3   So we have to be a little bit careful in using the mixed effect

4   model here when we have a very few observations on a particular

5   random effect that we're trying to model.

6   One other question I had related to random effects too, and I

7   should have asked it earlier, and that is is there any way that we can

8   reflect the degrees of freedom. And that is the statistical information

9   in these data set means and standard deviations.

10   In other words, the quantities going into these models are

11   actually estimates of means which are based on varying numbers of

12   individual observations on individual animal subjects.

13   And there is information there that in terms of degrees of

14   freedom that is not being reflected unless it's somehow being built into

15   as some sort of weighting for the actual variance of the mean that has

16   been estimated.

17   Finally, on the use of the profile likelihood, the whole issue of

18   data density arises here as well. We all know full likelihood is really a

19   function of the distribution that we assume. Here it is normal with a

20   conditional mean and defined by the exponential functions and the

21   amount of the individual data.

1   Look at the graphics that were presented in this report. And

2   they are excellent. I understand some of it has been redone, but I

3   wouldn't expect these conclusions to be completely overturned. When

4   there is data, the profile likelihood is very well defined. Obviously,

5   decisions to use a profile likelihood method to fix values of some of

6   these parameters that can't be separately estimated I think it makes

7   sense.

8   Other cases, though, and it generally happens when other parts

9   of the modeling break down, the profile likelihoods often wind up

10   being sort of ill-defined or somehow narrowed to a fairly wide plateau

11   on the likelihood function.

12   For example, I noticed very rarely, though, if the model fits well

13   to the data, and just by physical inspection, if the model fits well to

14   the data, these profile likelihoods are fairly well-defined.

15   If they're needed to fix values of these asymptotes for lowest

16   threshold or lower level of effect, I think that it is probably an

17   appropriate use.

18   Some things -- I only noted one case. And that was dichlorovos

19   where in the profile likelihood, and again, this may change with the

20   analysis that has been done subsequently, you get a saddle likelihood.

21   The model fits well, but the profile likelihood has this sort of saddle

1   shape.

2   So you don't know whether to go to Hill A or Hill B. You are

3   sort of stuck in the saddle in between.

4   Profile likelihoods for the expanded model when I looked at

5   those, they are -- when -- are informative at all, really. I felt they are

6   primarily limited to knowing that the displacement is a very small

7   number. And with a fairly wide range, don't do much to narrow the

8   region of the optimum on the shape function of the curve.

9   So essentially, it informs us a little bit about how large that

10   displacement might be in the model, but, again, leaves us pretty much

11   wide open with the data to choose an optimum S.

12   The benzylthide (ph) example which we saw in the screen here

13   and which I noted in my own notes was probably the exception. That

14   had the nicest sort of by more to likely or by very -- profile likelihood

15   for the expanded model.

16   In general, I would say that I think that as a general model, the

17   nonlinear mixed effect model is appropriate.

18   And in cases where we have a good number of studies and a rich

19   base of data that spans a wide range of doses, it appears to work well

20   and is clearly the preferred model.

21   I think like everything else in statistics when we begin to run

1   out of data, all of this begins to become a little more questionable.

2   And I really don't have any alternatives for those situations

3   where we're in the situation of sparse data, except to get more data,

4   and that doesn't help you right now.

5   DR. KENDALL: Thank you, Dr. Heeringa.

6   Dr. Portier, Dr. MacDonald?

7   Dr. Portier will go first.

8   DR. PORTIER: I will read the points I put down up to this

9   point.

10   I think the mixed effect model corrected for many of the

11   problems we highlighted in the previous review. So I think a lot of

12   things have been taken care of that we talked about.

13   In terms of the comment concerning the profile likelihood or

14   the question concerning the profile likelihood, my intuition in looking

15   at this is that if the optimization, if the algorithm used for

16   optimization dealt with boundary value problems, you would probably

17   skip that profile likelihood step.

18   It seems to me in the way you are doing the profile likelihood

19   visually and saying, well, this one is going to converge, but that one

20   doesn't, the failure to converge is at the boundary value situations.

21   And so it's the log transforms, the inability to go to actual zero

1   is the thing that may be driving the lack of convergence more so than

2   an actual failure to find an optimum.

3   And I think you should -- one suggestion is to look at that. I

4   don't think it will have any impact. Because the choices you are

5   making in the cases where you are getting stuck to the boundary is

6   exactly the choice in algorithm that dealt with the boundary value

7   problem we deal with.

8   I will reiterate that clarity of the model and methods would be

9   greatly appreciated. Again, showing a model in mathematical form

10   that talks about the variance construction and the fixed and random

11   effects that go on would be useful.

12   One point that comes to mind in hearing Dr. Heeringa's

13   comments just now is that in the decision tree where you were

14   evaluating how to move through the various models, it is a good

15   question to ask why go to a single B value with a random effect as

16   compared to a fixed sex effect B value as the third voice.

17   And the fact that you never choose the third choice may be

18   simply because the third choice and the second choice are effectively

19   equally parameterized.

20   And you would pick up the sort of almost the same likelihood in

21   the two separate cases.

1   And finally, one concern for me is the actual expanded model

2   itself. In essence, you have gone from the basic model to the

3   expanded model, and you have jumped in two parameters in doing it.

4   One parameter deals with sort of a shape issue and the other

5   parameter deals with sort of a point of discontinuity breakpoint off the

6   zero Y axis response point.

7   It might be interesting in thinking about how to move forward

8   with this to separate those two issues out and ask yourself do I really

9   need a shape parameter or do I really need a point of discontinuity on

10   the zero response point, and choose one or the other rather than

11   having to choose both in the analysis.

12   Because I am concerned about them collapsing in degrees of

13   freedom as they both get towards zero or infinity depending on the

14   parameter you are looking at in the expanded model.

15   DR. KENDALL: Any questions from EPA? Dr. Setzer?

16   DR. SETZER: I would like to respond. If I can remember the

17   points, I want to respond to a couple of those points.

18   As to the issue of basically -- the first part was sort of the issue

19   what is going on. How come we can't always estimate this horizontal

20   asymptote.

21   And Dr. Portier has said that it has something to do with -- has

1   to do with not being able to get to zero for the parameter on the right

2   scale.

3   One of the things I have done, since December, and it's not

4   anything you have seen or I didn't talk about it today because it is

5   complicated to describe, and I'm not sure how -- if it was worth

6   spending a lot of time on, but I'll bring it up.

7   There is an approach to analyzing parameter redundancy in

8   nonlinear models, which essentially looks at the degree to which over

9   the -- either for an experimental design or sort of over a range of the

10   independent variables, the degree to which parameters and the model

11   sort of -- multiple sets of values for the sets of parameters can give

12   you essentially the same model shape.

13   And I applied that to the specific designs we have in this study.

14   What happens is that the models where we have to fix a piece of

15   B or we have to affix B are exactly those chemicals where the degree

16   of association between the benchmark dose estimate and the piece of B

17   are highest.

18   So basically what happens is we could -- is that if you adjust

19   piece of B a little bit, you can also adjust the benchmark dose estimate

20   a little bit to give you essentially the model shape.

21   I don't think that is a function of the transformation used. I

1   think that's actually a function of the designs that we have to work

2   with.

3   I have forgotten my second point. So I'll let it go.

4   DR. KENDALL: Dr. Portier?

5   DR. PORTIER: I do agree that there are going to be cases

6   where the estimate of P of B is going to be so unstable that anything in

7   a broad range is going to work and you are going to get extremely flat

8   likelihoods. That should be reflected in the variance, not necessarily

9   in the convergence of the algorithm plus or minus error.

10   So the only problems I have ever seen in convergence of

11   algorithms for optimization are: One, I set my criteria for

12   convergence to be too tight.

13   Two, I have got multiple modes, I've got multiple humps. And

14   one time I get this one, another time I get that one.

15   And the third time is I have got nonidentifiability, and I just

16   don't know it. I have parameters that are so correlated with each

17   other that finding one value adjust the other value, and there is just an

18   infinite number of solutions, which is sort of what you are talking

19   about in the case of P B.

20   But the worst one I have ever found, the one that always hits me

21   is when I don't deal with the boundary value problem the way I should

1   deal with the boundary value problem. And I try to log transfer my

2   values and it keeps trying to go to negative infinity, and it just can't.

3   It can't ever converge because it just keeps chopping away little

4   pieces and parts.

5   And algorithms that specifically project you on to the boundary

6   and then send you along that boundary can converge quicker in those

7   situations than things that try to log transform you along that way.

8   I think it is worthwhile in future derivations of your code to

9   look for an optimization algorithm like a David and Fletcher Powell or

10   a gradient -- B F G S modified David and Fletcher Powell to deal with

11   the boundary conditions.

12   DR. KENDALL: Dr. Rhomberg?

13   DR. RHOMBERG: I hesitate to say this because we have been

14   already raising the question about how biologically interpretable the

15   shoulder equation is.

16   But if you send that all the way to zero by allowing yourself to

17   do that, by dealing with the boundary value like Dr. Portier is

18   suggesting, that is also, I think, equivalent to making K M equal to

19   zero.

20   And if that kind of a biological explanation is the cause for the

21   statistical problem which you have here, that causes all sorts of other

1   issues.

2   If there really is a detoxification step that gets saturated at such

3   low values that K M is not detectably different from zero, that's going

4   to affect the pharmacokinetics of other O Ps that are co-occurring.

5   And when they are not tested one by one, that's already an issue

6   that will come up later, I think.

7   And so I guess I would hesitate to say this is just an estimation

8   problem and we should let it go to zero if it wants to.

9   We should worry something about the biological basis of this,

10   even if we're not trying to turn it into a pharmacokinetic model to

11   make sure that we're not doing something statistically that would

12   cause it violence to the biological hypothesis of the reason for the

13   phenomenon in the first place.

14   DR. KENDALL: Thank you.

15   Dr. Conolly, Dr. MacDonald?

16   DR. CONOLLY: I think Lorenz just made a good point for why

17   you want to call it an empirical model. I think as long as you call it an

18   empirical model, then you don't have to worry about the interpretation

19   of K M too much.

20   Otherwise, I agree with Lorenz.

21   DR. KENDALL: Dr. MacDonald?

1   DR. MACDONALD: I agree pretty much with everything that

2   has been said so far. So I'm not going to repeat that.

3   But I think in talking with Dr. Setzer and listening to his

4   presentations, it is really a work in progress. You have made a lot of

5   changes since the material we got as a handout was prepared.

6   So I would assume that this isn't really the final version and

7   that you are going to continue to refine it. I think you will probably

8   have more success in fitting when you have tried a few more things.

9   Certainly, one advantage of working in R is that not only do you

10   have access to the source code, but you know who wrote it, and you

11   have access to the developers.

12   And generally speaking, they are very helpful if you want to

13   modify or improve it. So that's another very useful route to go.

14   This issue of whether to iterate on logs or on the original

15   parameters is something I have been dealing with in the last few

16   months. And what Dr. Portier and Dr. Setzer have said I agree with.

17   I don't have an answer yet, but it is just the sort of situation

18   where with experience you eventually do better.

19   I think, though, that we shouldn't get too hung up on the

20   inability to estimate all the parameters or even on the biological

21   reasonableness of the model.

1   I think much of this is a red herring. Because really, all we're

2   trying to get out of this is a BMD 10. In most cases, you don't need to

3   have accurate estimates of all the parameters to get a good BMD 10

4   out of it. The stability of that estimate is really what we need to be

5   looking at.

6   But it is a very elaborate mechanism that has been set up to get

7   one number when you have to get so many other numbers in the

8   process.

9   Though, certainly, the idea of using the mix model and

10   combining studies, that introduces the extra variances. But I think

11   they are of interest in their own right for the sorts of people that like

12   thinking about variability.

13   DR. KENDALL: Thank you. Any further comments to this

14   question?

15   Dr. Portier?

16   DR. PORTIER: I want to make sure a comment I made is not

17   lost. I think all of my comments will have minor impact on what is

18   actually done here.

19   I think the basic point for comment 1 B is that much of what we

20   wanted, much of what we asked for, has been done. And I think now

21   we're tweaking.

1   DR. KENDALL: Well said.

2   I guess the long story made short is you have done really well

3   since the last review and congratulations. I'm going to close this

4   session. We'll take a break. 15 minutes.

5   Dr. Perfetti, I would like to begin the assessment, the next

6   question, the hazard and dose response analysis.

7   Okay?

8   If you have any comments you want to make as we begin that.

9   DR. PERFETTI: Question 2?

10   DR. KENDALL: Yes.

11   Think about that after the break. That's what we will begin

12   with. So a 15 minute break. Thank you.

13   (Thereupon, a brief recess was taken.)

14   DR. KENDALL: We'll reconvene the SAP meeting to now the

15   session to deal with hazard and dose response analysis.

16   Dr. Perfetti has relayed to us he has no opening comments he

17   needs to make in order to encourage the panel to move forward.

18   I would like to ask EPA to put the Question 2 on the screen,

19   which they have done.

20   If they could read the question for us and then we will begin our

21   deliberation.

1   DR. LOWIT: An exponential model was utilized by the agency

2   in the July 2001 Preliminary Hazard and Dose Response Assessment of

3   the Organophosphate Pesticides. Based on the equation used in the

4   July document, cholinesterase activity decreases linearly in the low

5   dose region of the dose response curve.

6   Stakeholders present at the technical briefing in August of last

7   year and also a few members of the Science Advisory Panel from the

8   September meeting suggested that a flat low dose region may be a

9   more appropriate modeling approach. In response to this issue, EPA

10 has further investigated the shape of the low dose region of the dose

11 response curve.

12   Two versions of the exponential model were used in the

13 December hazard and dose response assessment. One version called

14 the basic model describes a linear low dose region and is similar to

15 the approach used in the July document. All 29 OPs were fit to the

16 basic model. A second version called the expanded model incorporates

17 two additional variables, shape and displacement, which describe a low

18 dose flat region.

19   The female brain cholinesterase data supported a flat low dose

20 region for eight OPs, which has now been revised to, I think it is, 17 --

21 17 once the errors in the code were fixed.

1   We would like you to comment on the mathematical derivation

2   of the expanded model in addition to the use of the profile likelihood

3   method for estimating the shape and displacement parameters when

4   they could not be estimated jointly with the other parameters.

5   DR. KENDALL: Thank you. Dr. MacDonald, you are to lead

6   off.

7   DR. MACDONALD: I feel that this has already been quite

8   fairly discussed in previous questions. I don't have a lot to add. In

9   fact, I used up my best ideas already.

10   So I'll just comment that I think that this model is very elegant

11   in the fact that it has a very simple biological basis. We don't have the

12   data to support anything more elaborate.

13   And I think with a little bit more experience we might have more

14   luck in fitting it over a wide year class of data sets.

15   DR. KENDALL: Thank you, Dr. MacDonald.

16   Dr. Harry?

17   DR. HARRY: As we were already trying to poll whether we

18   thought this had been covered or not, I think a number of us thought

19   that it had.

20   The only questions -- I like the biology that was behind trying

21   to come up with this. It seemed well thought out. And that was a very

1   impressive process -- and very difficult, I know.

2   The question that I had raised was based upon that, and I tried

3   to raise that earlier in the quality of the assays for comparison. And I

4   talked with Dr. Brimijoin over the break, and we were sort of talking

5   two different things when we were talking. And I feel very

6   comfortable with the assays that you guys are using for the enzyme

7   assays, that they are pretty comparable for potency chemical A to

8   chemical B on the assays.

9   My only hesitancy would be to cross that over to a lot of other

10   types of assays that may not be as equivalent between them.

11   But as far as the approach, like was mentioned, I think most of

12   your statisticians around the table have made their comments. I can

13   only come at it in a biology. And I was impressed with the thought

14   process that went behind trying to pull that out and getting that low

15   dose expression of what may be happening with that shoulder effect.

16   DR. KENDALL: Thank you. Dr. Rhomberg?

17   DR. RHOMBERG: I think also that most of my comments have

18   actually come up somewhere along the line already.

19   I guess I would like to just spend a second, though, reiterating

20   this notion that even though we're being empirical here, and I think

21   you made a very clear point of the fact that this is an empirical factor

1   that is not intended to be a physiologically based pharmacokinetic

2   model, it is only being inspired by some possible biological

3   explanation, that it is worthwhile thinking what biological

4   phenomenon could account for it in principle.

5   And do we know enough about them from other sources of data,

6   not from the shape of the dose response curve, to say whether that's

7   plausible or not.

8   And beyond whether it is plausible or not, if you invoke those

9   phenomena, what would those phenomena, then, say about other

10 situations. And I touched on this briefly before.

11   What this is basically saying is that the main pharmacokinetic

12 thing of concern here is other kinds of esterases in the liver that are

13 able to metabolize these things away before they really get a chance to

14 do their dirty work on acetyl cholinesterase inhibition.

15   How many of them are there? This is something I don't know

16 very well. How specific they may be.

17   But the possibility arises that if that is really the case that that

18 is going on, then low doses to some of these ones that have shoulders

19 big enough to sort of be in the shoulder region there, or getting to the

20 end of their shoulder region are saturating some of these enzymes.

21   And it will affect the way other compounds go in their relative

1   potencies.

2   What affect will that have on the compared potencies that

3   compounds have at the low doses where they are actually being

4   experienced compared to the BMD 10. And I think it is just

5   worthwhile thinking through those issues.

6   Not that you can do anything about them with dose response

7   data. I agree, you can't. But trying to bring some of these other

8   things in just sort of as a reality check I think is important.

9   It occurs to me that if this really is a pharmacokinetic

10   phenomenon, to a large degree it should probably also apply to the

11   same compounds for the RBC data. And not quite in the same way,

12   since, I suppose, there is not really a first past exactly in the same way

13   for the RBC, since it gets to the blood first no matter where once it

14   gets into the blood.

15   But nonetheless, this isn't really strictly a first past phenomenon

16   anyway. I think it really is just a matter of saturation of metabolic

17   clearance. That should apply to the same compounds for the RBCs.

18   And the question then is in looking at the RBC dose response

19   data, do you get the same kinds of things for the same compounds.

20   It would be interesting if you did. And if it was completely

21   different, it would make you wonder a little bit about the biological

1   interpretation of that phenomenon.

2   I think that the issue of actually estimating the two parameters

3   for this, we have gone on about a lot, and I think I have made my point

4   there as well, which is that for the purpose of just using this as an

5   empirical factor for the dose response curves, the difficulty in the S

6   and D issue doesn't really make an awful lot of difference.

7   The reason that it is difficult is because it doesn't make a lot of

8   difference. So it is not really something to be worried about too

9   much.

10   On the other hand, when the biological consequences of that, if

11   any, come into play, if they do, then those issues do become important,

12   the relative importance of S and D, because that influences the shape

13   at the low dose part of the curve, which is where small doses of the

14   OPs would be and where their relative potencies would actually be

15   coming into play. And that would be important to work through.

16   But I would encourage working those things through not with

17   the S and D that you fit by this empirical thing, but actually trying to

18   go to real pharmacokinetics to do it at that point.

19   That's all.

20   DR. KENDALL: Anything to add, Dr. Conolly?

21   DR. CONOLLY: No.

1   DR. KENDALL: Dr. Durkin?

2   DR. DURKIN: Again, a lot of what has been said covers this

3   topic.

4   I simply wanted to say that when I first looked at what you had

5   done, the term that crept to mind, not to get too technical, is I thought

6   it was cute as a button.

7   I did not have the chance to pop this into mathematic. I'm

8   assuming that the arithmetic is more or less correct.

9   And I thought you did a very nice job of making that transition

10   from we have an empirical model here but we tried to at least base it

11   conceptually on something biological.

12   I too agree that the best thing to do is a formal PB PK PD

13   analysis. I'm not really convinced we have the data yet to do that.

14   If you were to go away and work on this for another decade and

15   get the experimentalists involved in giving you the kind of information

16   that you need, you probably can do it at some point.

17   I don't know that you can do it now. I have poked around a bit

18   in the literature. I think there is stuff out there. I saw on a break --

19   Vicki was kind enough to at least give me a peak at some work that

20   you guys are doing that I think is worth pursuing on the PB PK PD

21   end.

1   But I think you did just a really nice job of admitting, frankly,

2   that we can't do a biologically based model. But you have come up

3   with an approach that I think is just fascinating to at least give us a

4   taste of a biological basis for the dose response model.

5   So I'm extremely happy with what I saw.

6   DR. KENDALL: Dr. Bull?

7   Thank you, Dr. Durkin.

8   DR. BULL: This is just to add. One of the things I noted is we

9   selected female brain cholinesterase activity inhibition because it was

10 empirically more sensitive.

11   Just to add a little bit I think to what Lorenz was saying, it

12 would be real nice to know how that played out in the male brain

13 cholinesterase. Because often, metabolic differences are accounting

14 for that and you might get some consistency or explanations for the

15 difference between the sensitivity in the male and female and be very

16 intellectually satisfying to say, yes, we picked the right one.

17   Otherwise, you are sitting there without really knowing a basis

18 of the difference in sensitivity. Up to this point in time, I looked at

19 your graph. I was pretty well convinced that the females are more

20 sensitive. But that doesn't mean that number 30 is.

21   So you kind of need to know what the basis of those things are

1   as you take it down to the next group of registered pesticides.

2   So it would be nice to know what the basis of that is.

3   DR. KENDALL: Any further comments? Dr. Portier?

4   DR. PORTIER: I was going over my notes from all the public

5   commenters to make sure that your promise that additional questions

6   that they wanted to ask the panel would be addressed by the panel, but

7   I don't see any other than the BMD 10 to BMD 01 question that

8   pertains to dose response.

9   The rest pertain mostly to exposure. So we'll deal with them

10   tomorrow.

11   I did have one comment, something for you to look at and think

12   about. I do not have an answer for. In looking at the expanded model

13   versus the basic model, you have eight cases where the expanded

14   model is significantly improved over the basic model, as I understand

15   what is presented to me in the tables.

16   And there may be a number of reasons why that occurs. But

17   let's talk about what it means. And I don't think you talked about what

18   it means. I think you talked -- you enumerated it for me, you pointed

19   out that there were these cases. But what does this mean in terms of

20   what is a general shape of a dose response curve for this type of effect

21   and this type of population.

1   Is there something that can be drawn out from that? For

2 example, you did 29 analyses. And so had you seen only one in 29

3 analyses that was statistically significant, one might conclude that this

4 is not major nonlinearity in the dose response for this type of pattern.

5   The fact that you see eight significant out of 29, and it's

6 actually less than that because some of them don't fit, does that tell us

7 something about the presence or absence of flat regions in the dose

8 response curve as a general rule in this data?

9   Had we addressed the data in the opposite way instead of

10 testing the hypothesis in the sense that we reject the higher order

11 nonlinear model in favor of the linear model, but going the other way

12 would we be looking at a different picture.

13   So I think as an agency you need to look at this and decide

14 would it be more appropriate even though overparameterized to use

15 the nonlinear or the more flexible model as a general rule in evaluating

16 these data simply because you see it eight times significantly better

17 across these data sets.

18   I don't have an answer, but I would love to see some discussion

19 of that in looking at what you are doing in here.

20   DR. KENDALL: Any further comments? Then that will

21 conclude our Session 1, hazard and dose response analysis.

1   Margaret, we are prepared to move forward to Session 2,

2   assessment of food exposure, should you want to.

3   DR. STASIKOWSKI: We would prefer to wait until tomorrow

4   morning to start the discussion.

5   DR. KENDALL: Could you be prepared tomorrow to be ready

6   to proceed through Section 2, assessment of food exposure and the

7   assessment of drinking water exposure?

8   DR. STASIKOWSKI: Yes.

9   DR. KENDALL: I think we will probably be able to get at least

10 through those two sessions, at least, if that would be possible.

11   DR. STASIKOWSKI: Yes. And if we're ready to start

12 residential, we'll be ready for that as well.

13   DR. KENDALL: Outstanding.

14   I ask the panel to get a good night's sleep. We may go further

15 than we think tomorrow.

16   Nevertheless, this has been an excellent day. Really incredible.

17   The word's incredible, the progress you have made. And quite

18 seriously, there have been no real serious criticisms outside of the fine

19 tuning and looking at procedure that can be best clarified and justified.

20   This will conclude our session today. And we will reconvene at

21 8:30 in the morning.

1   And I would like to ask if our designated federal official for the

2   meeting, who I have enjoyed working with, would like to have any

3   comments for the panel or other administrative issues.

4   MR. LEWIS: Thank you, Dr. Kendall, for moving us along

5   today and keeping us, if you will, ahead of schedule in allowing for a

6   good deliberation by the panel and for comments from a couple

7   commenters and allowing the presenters to move along at a good pace.

8   If I could ask all the panel members to reconvene in our

9   breakroom at 4:15, I just want to discuss with you about any

10   assistance you may need for compiling your comments and in terms of

11   drafting your responses as part of the discussion today. I would

12   appreciate it.

13   DR. KENDALL: This will close our session. Thank you.

14

15   - - -

16   [Whereupon, at 4 p.m., the

17   meeting concluded.]

18   -oo0oo-

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